A phase III randomized, double blind, placebo controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative AI treated, locally advanced or metastatic breast cancer who progressed on or after mTOR inhibitor based treatment

Published: 13-11-2012
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Primary: To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for all patients regardless of PI3K pathway activation status (unkown status...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON44929

Source
ToetsingOnline

Brief title
BELLE 3

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BKM120, breast cancer, fulvestrant, metastatic

Outcome measures

Primary outcome

Progression free survival.

Secondary outcome

Secondary: PFS based on ctDNA, Overall survival based on ctDNA, Overall

response rate based on ctDNA, Clinical benefit rate based on ctDNA, Safety, PK,

Quality of life, time to definitive deterioration of the ECOG PS of the score

of the baseline

Study description

Background summary

There are currently no treatments specifically approved for breast cancer after recurrence or progression on mTORi treatment. Hormonal therapy, in particular fulvestrant, remains one of the valid options in that setting.
A significant number of HR+ HER2- breast cancer patients are expected to have an activated PI3K pathway, either de novo (as diagnosed on archival samples) or after exposure to anticancer therapies. In these latter patients, PI3K pathway can be considered turned on irrespective of molecular alterations observed on archival sample. This pathway can play a critical role in inducing resistance to endocrine therapies and mTORi therapies. Promising pre-clinical and clinical

activity has been observed with single agent BKM120 in breast cancer together with the combined effect with fulvestrant in the pre-clinical setting.
Moreover, use of the pan PI3Ki BKM120 may be a way to overcome resistance to mTORi by targeting the PI3K pathway upstream. Therefore the addition of BKM120 to fulvestrant may be an effective treatment in HR+ HER2- MBC patients who have relapsed after mTORi treatment.
The purpose of this pivotal multi-center, double blind, two-arm, randomized phase III study is to determine whether treatment with BKM120 plus fulvestrant prolongs PFS compared to treatment with placebo plus fulvestrant in postmenopausal women with HR+ HER2- AI pretreated locally advanced or MBC whose disease has progressed on mTORi containing regimen for the following populations: i) all patients regardless of PI3K pathway activation status (unknown status is allowed) (full population) and ii) PI3K pathway activated sub-population.

Study objective

Primary: To determine whether treatment with BKM120 plus fulvestrant prolongs PFS based on local investigator assessment compared to treatment with placebo plus fulvestrant for all patients regardless of PI3K pathway activation status (unkown status is allowed) (full population) and for PI3K pathway activated sub-population.
Secondary: PFS based on ctDNA, Overall survival based on ctDNA, Overall response rate based on ctDNA, Clinical benefit rate based on ctDNA, Safety, PK, Quality of life, time to definitive deterioration of the ECOG PS of the score of the baseline

Study design

Multicenter randomized double blind placebo controlled parallel group phase III study.
Essay of existing or fresh tumor tissue for PI3K activation status.
Randomization (2:1) to treatment with:
• Fulvestrant 500 mg intramuscularly every 4 weeks (plus after 1st 2 weeks) + BKM120 daily 100 mg orally.
• Fulvestrant 500 mg intramuscularly every 4 weeks (plus after 1st 2 weeks) + Placebo.
Until disease progression.
Follow-up for survival.
Interim-analysis planned (see protocol section 10.7, protocol page 131).
Independent DMC.
420 patients

Intervention

Treatment with BKM120 or placebo in combination with fulvestrant.

Study burden and risks

Risk: Adverse events of study medication.
Burden: Study duration in principle until disease progression. weekly visits during 1st 2 courses of 4 weeks; 4-weekly thereafter. Follow-up for survival every 3 weeks.
Diary about medication intake during the whole study.
Physical examination every 4 weeks.
Blood draws 30-50 ml/week during treatment period.
PK blood sampling (2 ml/sample):
1st 100 patients:
• Day 1 course 1: 3-4 samples in 6-9 h.
• Day 15 course 1 and day 1 courses 2, 3 and 4: 1 sample.
Urine sample during screening.
ECG every 4 weeks.
Echocardiography or MUGA-scan every 12 weeks.
Tumor evaluations as during regular treatment, every 6 weeks.
Questionnaires (2 on mood changes, 2 on quality of life) (nearly) every visit.
Pregnancy test during screening and end of study.
Lung function test only if needed.
Tumor biopsy during screening (PI3K activation) only if no archival tumor material is available
Optional tumor biopsy 2x for biomarker research.
Optional availability of remaning tumor material for future research on BKM120 and/or breast cancer.

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Postmenopausal women breast cancer that is locally advanced or metastatic HER2 negative disease, and a known positive hormone receptor status (common breast cancer classification tests);Patient has adequate tumor tissue for the analysis of PI3K related biomarkers. Evidence of progression to the combination of mTORi and endocrine therapy given as the last therapy prior to study entry;Adequate bone marrow and organ function;Other protocol defined criteria may apply

Exclusion criteria

More than 1 prior chemotherapy given for locally advanced or metastatic disease;Previous treatment with PI3K inhibitors, AKT inhibitors or fulvestrant;Symptomatic CNS metastases;Concurrent malignancy or malignancy within 3 years prior to start of study treatment;Certain drugs or radiation within 2-4 weeks of enrollment - Increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent;Active heart (cardiac) disease or a history of cardiac dysfunction as defined in the protocol;Hypersensitivity to fulvestrant excipients;Certain scores on an anxiety and depression mood questionnaire given at screening;Other protocol defined criteria may apply

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-12-2013
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BKM120
Generic name:	buparlisip
Product type:	Medicine
Brand name:	Faslodex
Generic name:	fulvestrant
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	placebo
Generic name:	unknown

Ethics review

Approved WMO Date:	13-11-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-12-2012
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-04-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	10-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-08-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-08-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-01-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-04-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-05-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-09-2014

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-09-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	25-03-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-04-2017
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002571-34-NL
ClinicalTrials.gov	NCT01633060
CCMO	NL41871.068.12